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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/586,744	06/02/2000	John Joseph Harrington	9584-0017-999	7865

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EXAMINER	
SAIDHA, TEKCHAND	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/586,744	HARRINGTON ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,21-35 and 51-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 21-35 & 51-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Final Rejection

1. Applicants' amendment filed 20 May 2004 in this re-issue application is acknowledged. The original Patent No. 5,874,283, entitled 'Mammalian Flap-Specific Endonuclease', filed May 30, 1995, issued on February 23, 1999.

2. Claims 1-6, 21-35 & 51-76 are pending and under consideration in this examination.

3. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicants response and withdrawn.

4. A Third Party Protest [second protest] under C.F.R. 1.291 for this reissue application has been filed August 13, 2004, has been considered and is made of record.

5. Applicants letter filed 3.11.03 (Paper No. 32) and Offer to Surrender Patent is also acknowledged.

The original patent, or a statement as to loss or inaccessibility of the original patent, must be received before this reissue application can be allowed. See 37 CFR 1.178.

As per amendment filed May 30, 2004, Applicants propose to surrender the patent document once the claims are allowable.

6. Applicant's arguments filed as per the amendment cited above have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).

7. The reissue oath/declaration filed with this application is defective because it fails to identify at least one error which is relied upon to support the reissue application. See 37 CFR 1.175(a)(1) and MPEP § 1414.

The reissue oath/declaration filed with this application is defective because the error which is relied upon to support the reissue application is not an error upon which a reissue can be based. See 37 CFR 1.175(a)(1) and MPEP § 1414.

The nature of the defect(s) is that the 'error is not specific, nor is it an error correctable by re-issue'.

In accordance with 37 CFR 1.175(b)(1), a supplemental reissue oath/declaration under 37 CFR 1.175(b)(1) must be received before this reissue application can be allowed.

Claims 1-6, 21-35 & 51-73 are rejected as being based upon a defective oath/declaration under 35 U.S.C. 251. See 37 CFR 1.175. The nature of the defect is set forth above.

Receipt of an appropriate supplemental oath/declaration under 37 CFR 1.175(b)(1) will overcome this rejection under 35 U.S.C. 251. An example of acceptable language to be used in the supplemental oath/declaration is as follows:

> "Every error in the patent which was corrected in the present reissue application, and is not covered by a prior oath/declaration submitted in this application, arose without any deceptive intention on the part of the applicant."

Applicants' Response :

Applicants will submit such a supplemental oath once the claims are allowable. The rejection is maintained.

8. ***New Matter***

Claims 21-35 & 51-76 are rejected under 35 U.S.C. 251 as being based upon new matter added to the patent for which reissue is sought.

Applicant argue that 'It is well settled that amendments that replace subject matter incorporated into an application by reference with the **actual text and figures** of the incorporated document do not constitute new matter See, e.g., M.P.E.P 2163.07 (b).

By Applicants own arguments, it is acknowledged that replacing subject matter incorporated into an application by reference with the **actual** text and figures of the incorporated document do not constitute new matter. Therefore incorporation of the actual text or figures from Harrington and Lieber, 1995, J. Biol. Chem. 270 : 4503 would be proper. However, neither the issued patent (U.S.P. 5,874,283) nor the incorporated reference of Harrington and Lieber (1995), describe the method or hybridization complex forming steps of claims 21-35 & 51-76. Applicants may point to the actual text of the referred article of Harrington and Lieber (1995) or the issued patent in overcoming this rejection. There is no support in the instant specification or the incorporated reference that identifies the actual text which would indicate that the invention of claims 21-35 & 51-76 was **conceived at the time of filing this application**. Further there is no basis for methods of cleaving, detecting or formation of a hybridization complex or a kit - (Claims 21-35 & 51-76). It may also be noted that the incorporated reference shows cleaving of the DNA molecule (not RNA) therefore has no basis for 'polynucleotide' cleavage - RNA is not cleaved by FEN-1 (Harrington and Lieber, 1995, see page 1240, column 2, last 2 lines). Similarly there is no basis for

'polynucleotides' or 3' polynucleotides in the claims, whether it is for methods of cleavage or complexes or kits.

Effective incorporation by reference is lacking. Applicants must clearly point out where in specification (or issued patent) or in the properly incorporated reference such methods or complexes have a clear-cut basis, or the invention was conceived at the time of filing this application.

Applicants' Arguments:

Applicants argue that as explained during the personal interview on April 27, 2004, the 'adjacent polynucleotide is the "3' polynucleotide probe" is clearly defined in the reissue application at col. 11.17-24. Applicants further argue that the recited 5', 3'-double flap structure are cleaved by FEN-1 polypeptides.

In response, a method of cleaving a 5', 3'-double flap structure by murine FEN-1 (95% purified) is demonstrated by Harrington and Lieber, 1995, J. Biol. Chem. 270 : 4503, a reference that has been incorporated into this reissue application. The "3' polynucleotide probe" is defined in the reissue application at col. 11.17-24. However, no clear-cut method steps for 'detecting the presence of a predetermined target nucleic acid' [claims 21-35]; or a 'hybridization complex' [claims 51-58]; or a 'kit for detecting a target nucleic acid' [claims 59-76] as claimed are described either in the instant specification of this reissue application or in the incorporated Harrington and Lieber (1995) reference. This issue was not addressed by the Applicants.

The new matter rejection is maintained for lacking incorporation of the actual text from Harrington and Lieber, 1995, J. Biol. Chem. 270 : 4503.

As pointed out above the incorporated reference shows cleaving of the DNA molecule (not RNA) therefore has no basis for 'polynucleotide' cleavage - RNA is not cleaved by FEN-1. Applicants have not addressed this issue. If Applicants are assuming a species/genus issue, wherein a species 'DNA' is taught and 'RNA' being within the scope of a skilled artisan, the examiner would disagree, because it is the double flap DNA that is cleavable not the RNA. The new matter rejection is maintained for this reason as well.

It is noted that Applicants' have amended claims reciting nucleotide ranges 1-10 and 1-20. The specification has been checked to the extent possible for improper incorporation of nucleotide ranges. However, Applicants' cooperation is sought in deleting the incorporation of these nucleotide ranges into the instant specification.

9. ***Written Description***

Claims 21-25, 31-35, 51-68 & 74-76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to a method of detecting the presence of target nucleic acid (claims 21-25, 31-35 & 74), a hybridization complex (claims 51-58 & 75) and a kit for detecting the presence of a target nucleic acid (claims 59-68 & 76). The instant claims contain no limitations that define the structures of the endonuclease (or FEN-1 SEQ ID NO :), or the double flap FEN-1 substrate, used for cleaving a polynucleotide comprising the 3' and 5' regions or that used in the detection method or

for hybridization complex and kit. The incorporated reference of Harrington and Lieber, 1995, J. Biol. Chem. 270 : 4503, shows cleavage of 3',5'-double flap structure using Murine FEN-1 only.

While the specification describes four species of purified FEN-1 polypeptides viz., human FEN-1 (SEQ ID NO : 1), murine FEN-1 (SEQ ID NO : 3), yeast FEN-1 (SEQ ID NO : 5) and the endonuclease activity of RAD2 : SEQ ID NO : 7; and crude extracts of calf thymus, rabbit reticulocytes, Chinese hamster fibroblasts and Drosophila embryos have also been shown to possess FEN-1 activity. Although these species though have been shown to have FEN-1 activity, 3',5'-double flap cleavage activity is only been demonstrated in FEN-1 from murine, which is not representative of the entire 'FEN-1' 3',5'-double flap cleaving (or hybridizing) genus.

Thus there is no disclosure of any particular structure to function/activity relationship in the disclosed species. The specification also fails to describe additional representative species of the polynucleotide probes by any identifying structural characteristics or properties other than stating that they are capable hybridizing under undescribed conditions and for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Arguments :

Applicants argue that the instant application describe a representative number of species of endonucleases adequate to provide written description support for the genus. For example, the disclosure describes four species of FEN-1 polypeptides : human FEN-1 (SEQ ID NO : 1), murine FEN-1 (SEQ ID NO : 3), yeast FEN-1 (SEQ ID NO : 5) & SEQ ID NO: 7. Further species of FEN-1 isolated from nuclear extracts of calf thymus, rabbit reticulocytes, Chinese hamster fibroblast and Drosophila embryos are described. These species adequately represent the genus of suitable endonucleases.

Applicants arguments having been considered in the light of the interview [April 27, 2004], as well as amendment filed May 30, 2004, but not found persuasive because of the following reasons:

Although 4 purified FEN-1 sequences of SEQ ID Nos. 1, 3, 5 or 7 and **four crude or nuclear extracts [obviously with no structure]** have been shown to have FEN-1 activity, only murine FEN-1 (SEQ ID NO: 3) has been shown to cleave 3',5'-double flap structure of Figure 12. Further, Applicants have not shown or described how the single species is representative of the entire genus of FEN-1. The structures of four FEN-1 is known, which however, is insufficient to be representative of the entire genus, because neither their structures are known to bear close similarity among each other nor have the various FEN-1 been shown to cleave 3',5'-double flap structure [with the exception of murine FEN-1 of SEQ ID NO: 3]. In essence, a single species (murine FEN-1) has been described to cleave the double flap structure of Figure 12, which is insufficient to be representative of the entire genus. Even if all the eight species of FEN-1 were known to cleave 3',5'-double flap structure, it would still be not representative of the entire

genus, because, such a genus would still encompass FEN-1 from hitherto undescribed or undisclosed sources, and for which no predictability of structure is apparent.

Likewise in the instant case, claims drawn to a method of cleaving a 5'-polynucleotide by FEN-1 do not functionally or structurally define the double flap structure used as substrates in the method [nor are structures well known in the art prior to the instant filing], for being acted upon by the FEN-1 polypeptide, and that the determination of suitable substrates or double flap structures would require testing by trial and error many known or unknown double flap structures to ascertain those which would function in the manner required by the claims, and would involve undue burden upon those skilled in the art.

Therefore, Applicants' arguments citing *University of Rochester v. G.D. Searle & Co. Inc.*, [wherein – A method patent for treating the side effects of pain relievers is invalid for failing to adequately describe the compound used in the claimed method, the U.S. District Court for the Western District of New York rules. Granting a summary judgment motion, the court reasons that the written description requirement of 35 U.S.C. §112 ¶1 cannot be satisfied by merely providing the desired function of the compound without more detail on the compound's structure, chemical formula, chemical name, or physical properties. The court also stresses the applicability of the written description requirements to the compound used, even though the patent consists of method claims rather than compound claims. *University of Rochester v. G.D. Searle & Co. Inc.* Page 427], do not have a bearing in the instant case in view of reasons discussed. Further, as

may be seen, not all claims are 'method claims', and cannot be grouped together in arguing the Rochester decision.

In the instant case Applicants have failed to articulate in describing the double flap structure of Figure 12, the compound in question. Similarly, Applicants' claimed method of detecting the presence of target nucleic acid (claims 21-25, 31-35 & 74), a hybridization complex (claims 51-58 & 75) and a kit for detecting the presence of a target nucleic acid (claims 59-68 & 76) remain undescribed for lack of description of any FEN-1 capability to cleave any double-flap structure(s) as well as lack of description of the "3',5'-double flap structure" itself.

10. No claim is allowed.

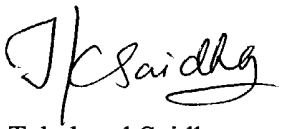
11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272 0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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